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Chronic Fatigue Syndrome: What do we Know About its Aetiology & Treatment?

Yasir Abbasi [1], Waqqas Khokhar [2], Mohammed Mubashir Ali[3]

[1] North Derbyshire Mental Health Services, Chesterfield Royal Hospital
[2] Mid Trent Psychiatric Rotation, Lincolnshire Partnership NHS Foundation
[3] Wathwood Medium Secure Unit, Nottinghamshire Healthcare NHS Trust

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Abstract

The historical development of the concept of chronic fatigue syndrome (CFS) as a disease entity as well as the proposed management strategies has been contentious. This illness which is ever-growing has significant social, personal and economic costs for the society in general and the individuals suffering from it in particular. We acknowledge the heterogeneity of this syndrome and attempt to highlight the current evidence base around the aetiological hypothesis of this 'mysterious' illness. Finally the treatments that can potentially affect the course, outcome and quality of life of the sufferers are discussed. The article calls for further research and development in order to reach a consensus on the diagnostic criteria and the determinants of biological and psychological parameters to serve as markers of treatment response.

Key words: Chronic Fatigue Syndrome, Gulf War Syndrome, CBT, Psychiatric Co-Morbidity, Genetics, Myalgic Encephalomyelitis.

Introduction

Chronic fatigue syndrome (CFS), also known as Myalgic Encephalomyelitis (ME) or post viral fatigue syndrome, is not a new entity. In the 19th century a neurologist, George Beard (1869), used the term neurasthenia and nervous exhaustion for a condition resembling that of CFS. The term myalgic encephalomyelitis has also been used for symptoms resembling that of CFS in medical literature and was described in detail by Ramsay (1978).

CFS has, to a certain extent, been a contentious diagnosis, especially with regards to its clinical definition and aetio-pathogenesi. Chronic Fatigue Syndrome fell into controversy again when the 1991 Gulf War Veterans complained of symptoms resembling those of CFS. Their illness was later dubbed Gulf War Syndrome (GWS). However, large cohorts studied ten years after the first Gulf War did show that the veterans were at increased risk of Fibromyalgia, CFS and other medical illnesses (Eisen et al, 2005).

The Centre for Disease Control (CDC) in 1988 introduced the term chronic fatigue syndrome (Holmes et al, 1988). Later, they used the term chronic fatigue and immune dysfunction syndrome (CFIDS) in an attempt to reduce the psychiatric stigma often associated with CFS (Jason et al, 2005). CFS is classified under Chapter 6 (G Code) of the International Classification of Diseases-10th edition, i.e. Diseases of the Nervous System (WHO, 1990).

Most definitions warrant a number of features to be present before a diagnosis can be made. The most common being severe mental and physical depletion for more than 6 months which, according to Fukuda et al (1994), is unrelieved by rest, and is usually made worse by even trivial exertion. There is, however, no consistent method which would allow objective measures, such as blood tests or brain scans, to diagnose CFS with certainty. Unsurprisingly, therefore, the biggest hurdle encountered in the management of CFS is the diagnosis. There are numerous symptoms which patients can experience but the common ones include cognitive

difficulties (short term memory loss), sore throat, myalgia, lymphadenopathy, arthralgia and fatigue following exertion, lasting for days. The above should usually be present for longer than six months according to the CDC criteria as well (Holmes et al, 1988).

A recent review by Cho et al (2006) concluded that more research is required to improve the current case definition, as investigations overlap and boundaries among various functional somatic syndromes are fluid. This should help us to understand whether the pathophysiological findings in CFS are a cause or consequence of illness, as well as clarifying the interplay between the central nervous system, immunological and genetic factors.

Aetiology:

A variety of factors have been hypothesized in the aetiology of CFS (Table 1) but to date, no definitive cause has been singled out. Hypotheses regarding the causes of CFS are discussed below:

Table 1

Possible Aetiologies for Chronic Fatigue Syndrome:

Hormonal and Central Nervous System factors
Viral or other infectious agents and immune dysfunction
Genetic Factors
Psychiatric co-morbidity
Other Factors i) Sleep Disturbance ii) Exercise Intolerance iii) Neurally Mediated Hypotension iv) Hyperventilation

1. Hormonal and Central Nervous System Factors:

Cleare (2004) suggested that there is under-activity of the hypothalamopituitary-adrenal (HPA) axis in most patients diagnosed with CFS. This leads to a lower cortisol level, suggesting an endocrinological basis to the illness. Another study by Cleare et al (1999) on the diurnal patterns of salivary cortisol and cortisone output in chronic fatigue syndrome provides further evidence for reduced basal HPA axis function in at least some patients with CFS.

2. Viral or Other Infectious Agents and Immune Dysfunction:

According to De Becker et al (2002) three-quarters of patients with the disorder have reported an infection, such as a cold, flu-like illness, or infectious mononucleosis, as the trigger. White et al (2001) found a causal relation between infectious mononucleosis and chronic fatigue. Ablashi (1994) thought that Epstein-Barr virus, human herpes virus 6, group B Coxsackie virus, human T-cell lymphotrophic virus II,

hepatitis C, enteroviruses, and retroviruses were of significance in chronic fatigue syndrome, implying a damaged immune system resulting from infection. Other organisms have also been implicated and particularly high rates of chronic fatigue have been found following Q-fever and Lyme disease. However, Swanink et al (1995) found no differences in viral loading of Epstein-Barr virus and immunological reactivity between individuals who developed CFS and those who did not. Not all CFS sufferers show signs of previous infection and experts remain divided as to whether infection has any causative role in the disorder.

Another study (Peakman et al, 1997) focused on cytokines and shifts in T-lymphocyte subsets with variable results. A study of monozygotic twins discordant for CFS (Sabath et al, 2002) also failed to provide support for immunological abnormalities.

3. Genetic Factors

A twin study done by Buchwald et al (2001) has shown a familial predisposition where the concordance rates were higher between monozygotic than dizygotic twins. They suggested that interaction between genetics and environment plays an important role in the aetiology of CFS. Similarly, Sullivan et al (2005) in a study of twins in a Swedish national sample concluded that illness with marked symptoms of chronic fatigue appears to result from both environmental and genetic sources of variation, without pronounced differences in gender. Smith et al (2005), found that CFS might be associated with HLA DQA1*01 locus.

4. Psychiatric Co-Morbidity

This has been controversial with certain researchers believing CFS to be primarily a functional illness (Stewart 1990) while others affirm that it has many organic components. Indeed, CFS sufferers have a higher incidence of psychiatric morbidity including severe depressive disorder (Manu et al 1989); generalised anxiety disorder (Kruesi et al, 1989), and somatoform disorder (Manu et al, 1993). According to Johnson et al (1996), if healthcare professionals attribute CFS to physical rather than psychiatric disorder, the rate of diagnosis falls dramatically. This is especially true of somatoform disorders. More research is needed on the temporal relationship between chronic fatigue symptoms and psychiatric illness.

5. Other Factors:

- **Sleep Disturbance** - According to Krupp et al (1993) sleep disruption does not appear to correlate with fatigue severity but at the same time they concluded that subjective sleep disturbance is common in CFS and some patients may have sleep disorders.

- **Exercise Intolerance** - It is a possibility that patients with CFS might have some intrinsic inability to tolerate exercise. Lane et al (1998) suggested increase in lactic acid in response to exercise, while Wagenmakers et al (1988) felt that a reduction in number of muscle mitochondria is likely to be blamed for the reduced exercise intolerance. These findings are in the process of being validated by larger studies.

- Neurally Mediated Hypotension – Wilke et al (1998) formulated after combining the results from various related studies that some patients diagnosed with CFS

have abnormal vasovagal or vasodepressor responses to upright posture. These findings, if validated, by larger controlled trials may help explaining some of the somatic symptoms of CFS.

- Hyperventilation - Hyperventilation has also been theorised to play a causal or maintaining role in CFS. Van der Meer et al (1997) suggested that there was more physiological evidence for hyperventilation in patients with CFS than healthy individuals but that it should be regarded as an epiphenomenon. However, earlier suggestions in a study by Saisch et al (1994) only indicated a weak association between hyperventilation and CFS.

Treatments

There are a number of options and approaches which can be used for the treatment of CFS (Table 2). However, the emphasis should be on a tailored approach to suit individual needs and requirements. Maquet et al (2006) suggested that a bio psychosocial approach and progressive muscular rehabilitation combined with behavioural and cognitive treatments should form an essential part of the holistic approach in managing the heterogeneous symptoms of the CFS complex.

Table 2

Different treatment options

Biological	Antidepressants Corticosteroids Immunoglobulin Anti-viral & Anti-Microbial Others
Psychological	CBT
Non-Pharmacological	Graded Exercise Therapy (GET) Activity Management Sleep Management Relaxation Techniques

1. Non- Pharmacological approach

- **Graded Exercise Therapy:** Saggini et al (2006) proposed that rehabilitative exertion was a useful treatment for CFS patients. In another study Van der Meer et al (2005), also established that exercise improved fatigue symptoms in CFS patients but there was no change in overall level of activity. Rimes et al (2005) did a literature review to evaluate the treatment options available for CFS and found promising results with graded exercise combined with cognitive behaviour therapy.

- **Cognitive Behavioural Therapy**: There is growing evidence to support the use of CBT either alone or in combination with other forms of treatment in CFS. In a randomised control trial Deale et al (1997) observed a 70% improvement in physical activities in patients with CFS who received 13-16 sessions of CBT as compared to controls who received relaxation therapy. Chisholm et al (2001) also concluded that counselling and CBT, both showed improvement in fatigue

and related symptoms. In a multicentre randomised controlled trial Prins et al (2001) observed that CBT was more effective than guided support groups. These improvements are noted to have been sustained over a period of 6-14 months.

2. Pharmacological Approach

- **Antidepressants**: Psychiatrists are often called in to help managing the symptoms of CFS by the multi-disciplinary team especially where the affective symptoms are a cause of concern. White et al (1997) studied the effects of moclobemide on CFS and suggested that in the absence of a co-morbid depressive disorder, the use of this medication should be limited. Hartz et al (2003) in a randomised controlled trial studied the effects of Citalopram in patients with idiopathic chronic fatigue. They measured the improvement in CFS sufferers with the Rand Vitality index and concluded that Citalopram may improve fatigue and symptoms associated with fatigue for some patients. However, there is no conclusive evidence to support the use of antidepressants in CFS.

- **Corticosteroids**: In a randomised controlled clinical trial Cleare et al (1999) used low dose Hydrocortisone to reduce fatigue in the short term. However, Blockmans et al (2003) in a randomised, placebo-controlled, double blind crossover study concluded that low-dose combination therapy of hydrocortisone and fludrocortisone was not effective in patients with chronic fatigue syndrome. Long term, follow up studies are required to see if any benefits achieved are long lived and clinically useful.

- **Immunoglobulin**: It is only natural to explore the role of Immunoglobulin since immune dysfunction has been hypothesised as a potential factor in the aetiology of CFS (Ablashi, 1994). In a randomized, double-blind, placebo-controlled trial to determine the effectiveness of high-dose intravenously administered immunoglobulin G, Lloyd et al (1990) found that immunomodulator treatment with immunoglobulin is effective in a significant number of patients with CFS.

- **Antiviral & Antimicrobial**: There is weak evidence that such treatments would help, as no infectious cause has been established yet. Acyclovir has been found to be ineffective (Straus et al 1988; Iwakami et al 2005).

- **Other Treatments**: The use of Essential Fatty Acids (Warren et al 1999), reduced form of oral nicotinamide adenine dinucleotide (Forsyth et al 1999) and Selegiline (Natelson et al 1998) has been of little value without any promising results. An experimental medication Ampligen, a synthetic nucleic acid Poly(I).Poly(C12U) is being studied for potential use in patients with CFS.

3. Alternative Approaches

When symptoms are unrelieved by conventional medicine, it's not uncommon for sufferers of CSF to turn to alternative and or complementary methods. These treatments include megavitamins; herbal therapies; special diets and adenosine monophosphate, iron, magnesium sulphate, melatonin and zinc supplements (Jens, 2005). However, randomised control trials to determine the effectiveness of these treatments are almost nonexistent.

Conclusion

Chronic Fatigue Syndrome is heterogeneous in presentation and this may point towards a similar aetiology. It would therefore, require a multi-disciplinary approach to diagnosing and treating the intriguing symptoms of this 'mysterious' illness. Especially, when there is still some doubt and stigma attached to the very process of diagnoses and the sufferers alike (Jason, 2004).

The support of the scientific community to undertake further research into exploring this multi-faceted illness is imperative to achieve the above mentioned aims. The first hurdle for patients is being diagnosed. Therefore, serious attempts should be made to develop universally acceptable and applicable diagnostic criteria. The importance of identifying a range of biological and psychological parameters as markers for treatment cannot be undermined either. The increased variety of outcome measures used in the studies quoted in this article makes standardisation of outcomes a priority for future research.

The second hurdle is to get the right help from the right services and appropriate management for it. At the moment most patients in England and Wales are managed either by their GP's or referred to psychiatrists and/or neurologists for advice. Instead, there is a need to develop specialist services for these patients, which can provide holistic input in managing CFS with emphasis on graded activity and exercise and collaboratively work with the patients to develop individually tailored recovery plans. Hence, we need to remodel our current services and build specialist diagnostic and rehabilitation centres for CFS sufferers all over the country, like the one established by Barking, Havering and Redbridge University Hospitals NHS Trust. (http://www.bhrhospitals.nhs.uk/cfs/cf1.php).

Chronic Fatigue Syndrome has survived the test of time and is likely here to stay as a complex illness. It is therefore essential that the 'true' prevalence of this illness in the community is recognised and determined sincerely. This can be achieved by setting up multi-site epidemiological studies across the world.

It is also imperative that good care of our patients, integrate medical and psychological concepts, together with symptomatic management. This may help to prevent significant secondary impairment in the majority of patients and could help to improve the quality of life of the sufferers.

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